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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,448	11/07/2001	David Lewis	Mirus.030.03	3784

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
06/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/007,448	LEWIS ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2007 and 22 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-9, and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed September 28, 2007 and Applicant's Remarks filed February 22, 2008.

Claims 9 and 13 have been canceled. Claims 1, 3, 5, 14, and 15 have been amended.

Claims 1, 3-9, and 14-16 are pending in the instant application.

Claims 1, 3-9, and 14-16 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Remarks

Applicant's Remarks filed February 22, 2008 are acknowledged. It is noted that in Office Actions mailed June 16, 2004 and November 23, 2004, Applicant received actions on the merit for a process for delivering a polynucleotide into a cell of a mammal to inhibit protein expression. Since this invention was searched and examined earlier during prosecution, it would not require a distinct search to examine such claims as now presented. In this regard, Applicant's invention, now drawn to a process for delivering a RNA into a cell of a mammal to block protein expression will be fully considered, searched, and examined on the merits.

Priority

In the previous Office Action mailed August 22, 2007, the claimed invention was

afforded priority USSN 09/447,966, now U.S. Patent No. 6,627,616, filed November 29, 1999 because support for the claims, drawn to a process for delivering, without a transfection reagent used in the prior art, a polynucleotide into a cell of a mammal to inhibit, eliminate, or alter expression of an endogenous nucleotide sequence could not be found in any earlier application which Applicants claim priority to. It should be noted that Applicants have amended the instant claims to be drawn to a process for delivering a RNA into a cell of a mammal to block the production of a protein. Given the claims as now amended, the claimed invention has been afforded priority to the filing date of U.S. Patent No. 6,265,387, filed November 21, 1997.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed August 22, 2007, claims 1, 3-9, and 13-16 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is moot** against claims 9 and 13 in view of Applicant's Amendment filed September 28, 2007 to cancel these claims. **This rejection is withdrawn** against claims 1, 3-9, and 14-16 in view of Applicant's Amendment filed September 28, 2007. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to correct for a lack in antecedent basis.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed August 22, 2007, claims 1, 3-6, 8 and 13-15

were rejected under 35 U.S.C. 102(b) as being anticipated by Kumasaka et al. (Journal of Clinical Investigation, 1996 Vol. 97:2362-2369, made of record in the Office Action filed November 23, 2004). **This rejection is moot** against claim 13 in view of Applicant's Amendment filed September 28, 2007 to cancel this claim. **This rejection is withdrawn** against claims 1, 3-6, 8, 14, and 15 in view of Applicant's Amendment filed September 28, 2007. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to have the invention be directed to a process for delivering a RNA into a cell of a mammal to block the production of a protein.

In the previous Office Action mailed August 22, 2007, claims 1, 3-6, 8, and 13-16 were rejected under 35 U.S.C. 102(b) as being anticipated by Graham et al. (Journal of Pharmacology and Experimental Therapeutics, 1998 Vol. 286:447-458, made of record in the Office Action filed November 23, 2004). **This rejection is moot** against claim 13 in view of Applicant's Amendment filed September 28, 2007 to cancel this claim. **This rejection is withdrawn** against claims 1, 3-6, 8, and 14-16 in view of Applicant's Amendment filed September 28, 2007. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to have the invention be directed to a process for delivering a RNA into a cell of a mammal to block the production of a protein.

In the previous Office Action mailed August 22, 2007, claims 1, 3, 4, 5, 7, 9, and 13-15 were rejected under 35 U.S.C. 102(e) as being anticipated by Kay et al. [U.S. Patent No. 6,107,027, made of record in the Office Action filed November 23, 2004].

This rejection is moot against claims 9 and 13 in view of Applicant's Amendment filed September 28, 2007 to cancel these claims. **This rejection is withdrawn** against claims 1, 3, 4, 5, 7, 14, and 15 in view of Applicant's Amendment filed September 28, 2007. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to have the invention be directed to a process for delivering a RNA into a cell of a mammal to block the production of a protein.

Applicant's Amendment filed August 22, 2007 necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-5, 7, 8, and 14-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Kay et al., U.S. Patent No. 6,107,027, of record.

Claim 1 is drawn to a process for delivering a RNA into a cell of a mammal to block the production of a protein comprising making the RNA consisting of a sequence that is substantially complementary to a nucleic acid sequence in the mammal; inserting the RNA into a vessel in the mammal, wherein the vessel consists of arteries, arterioles,

capillaries, venules, sinusoids, veins, lymphatics, and bile ducts; and delivering the RNA to the cell wherein the protein production is blocked. Claims 3-5, 7, 8, and 14-16 are dependent on claim 1 and include all the limitations of claim 1 with the further limitations wherein vessel permeability is increased by increasing pressure against vessel walls by increasing a volume of fluid within the vessel, wherein increasing the volume consists of inserting the RNA in solution into the vessel; wherein the vessel is a bile duct, wherein the vessel is a liver vessel; wherein the cell is selected from a liver, spleen, heart, kidney, muscle or lung cells; wherein the pressure increases organ volume; and wherein the pressure is sufficient to increase extravascular volume.

Kay et al. disclose a method for inhibiting hepatitis C virus (HCV) RNA in cells comprising administering an adenovirus encoding a HCV ribozyme, which inhibits the hepatitis C virus (see claim 1). Kay et al. disclose the adenovirus encoding a HCV ribozyme, which inhibits the hepatitis C virus RNA, is infused via the bile duct (see claims 1 and 7), inhibits viral RNA in hepatocyte cells (see claims 1 and 2), and inhibits hepatic mRNA expression in transgenic mice (see Figure 4B). Kay et al. further disclose that their invention provides methods for treating or preventing hepatitis C infection in a mammal using ribozymes that can be administered to the liver of a mammalian individual (see column 4, lines 9-13, for example).

It is noted that injection into the bile duct with the adenovirus encoding a HCV ribozyme is equivalent to increasing vessel permeability within the vessel, by increasing pressure against vessel walls, increasing a volume of fluid within the vessel, and increasing extravascular volume as claimed because the method of injection would

inherently increase pressure in the area of injection and at the point of injection. The pressure against the vessel walls would inherently be increased because the needle used is external to the bile duct. It is further noted that Kay et al. are silent regarding the effect of the adenovirus encoding a HCV ribozyme on protein expression. However, given the inhibition of hepatic mRNA in transgenic mice by the adenovirus encoding a hepatitis C virus ribozyme, one of skill in the art would conclude that inhibition of protein expression would result to some degree, absent evidence to the contrary.

Therefore, absent evidence to the contrary, claims 1, 3-5, 7, 8, and 14-16 are anticipated by Kay et al.

Response to Arguments

It is noted that a similar rejection was made of record in the Office Action mailed June 16, 2004. In response to this rejection, Applicants submitted a § 1.131 Declaration to attempt to establish invention for delivery of short polynucleotides prior to the effective date of the Kay reference. However, it should be noted that this Declaration is not sufficient to obviate the instant rejection because claims 1, 3-5, 7, 8, and 14-16 are drawn to a process for delivering a RNA into a cell of a mammal to block the production of a protein. Kay et al. disclose a method for inhibiting hepatitis C virus RNA in cells comprising administering an adenovirus encoding a HCV ribozyme, which inhibits the hepatitis C virus RNA, wherein the ribozyme is infused via the bile duct (see claims 1 and 7). Applicant's §1.131 Declaration is partly directed to a process of delivering siRNA to a cell of a mammal via high-pressure tail vein injection and partly directed to a

process of delivering DNA oligonucleotides to a cell *in vitro*.

The first issue is that Kay et al. teach the delivery of a RNA to the **bile duct** and Applicant's §1.131 Declaration shows results from experiments using only **tail vein injection**.

The second issue is the Kay et al. patent was filed on September 11, 1995 and Applicant's instant invention has been afforded priority to November 21, 1997. Applicants contend that the §1.131 Declaration establishes invention for delivery of short polynucleotides prior to the effective date of the cited reference. It should be noted that the Examiner is assuming that the short polynucleotides that Applicants are speaking of are siRNA since the §1.131 Declaration is largely directed to the delivery of siRNA, as it relates to inhibiting or blocking expression.

It is well known in the art that siRNA technology is a relatively new art. In fact, one of the earliest publications concerning delivery of double-stranded RNA (dsRNA) to inhibit target expression in a mammal is that of Wianny and Zernicka-Goetz (Nature, 2000 Vol. 2:70-75). For example, Wianny and Zernicka-Goetz teach dsRNA-mediated inhibition of gene expression and RNAi offers new opportunities to study loss-of-function phenotypes in specific cells and at specific stages of development of the early mouse embryo.

In short, in view of the fact that Kay et al. teach delivery of a RNA to the bile duct and Applicant's §1.131 Declaration addresses only tail vein delivery, the §1.131 Declaration has not been found persuasive. Additionally, in view of the fact that Applicant's §1.131 Declaration is largely directed to a process of delivery of siRNA, of

which was not known until at least 2000, the §1.131 Declaration has not been found persuasive to overcome the effective date of the reference of Kay et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumasaka et al. (Journal of Clinical Investigation, 1996 Vol. 97:2362-2369, of record).

Claim 1 is drawn to a process for delivering a RNA into a cell of a mammal to block the production of a protein comprising making the RNA consisting of a sequence that is substantially complementary to a nucleic acid sequence in the mammal; inserting the RNA into a vessel in the mammal, wherein the vessel consists of arteries, arterioles, capillaries, venules, sinusoids, veins, lymphatics, and bile ducts; and delivering the RNA to the cell wherein the protein production is blocked. Claim 6 is dependent on claim 1

and includes all the limitations of claim 1 with the further limitation wherein the vessel consists of a tail vein.

Determining the scope and contents of the prior art

Kumasaka et al. teach a process for delivering an antisense oligonucleotide, ISIS 3082, into a cell of a mammal via intravenous injection. Kumasaka et al. teach that ICAM-1 mRNA expression was detected and inhibited in the lung (see Figures 1 and 2). Kumasaka et al. disclose ISIS 3082 was injected into BALB/C mice through the tail vein and neutrophil emigration was detected in the lungs (see Figure 4). It is noted that Kumasaka et al. are silent regarding the effects of ISIS 3082 on protein expression. However, given the inhibition of ICAM-1 mRNA expression by ISIS 3082, one of skill in the art would conclude that inhibition of protein expression would result to some degree, absent evidence to the contrary.

Ascertaining the differences between the prior art and the claims at issue

Kumasaka et al does not teach delivering a RNA into a cell of a mammal. However, the skilled artisan would have known that an antisense oligonucleotide and a RNA used for blocking protein production are known equivalents in the pertinent art.

Resolving the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

Considering objective evidence present in the application indicating obviousness or nonobviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to devise a process for delivering a RNA into a cell of a

mammal to block the production of a protein comprising making the RNA consisting of a sequence that is substantially complementary to a nucleic acid sequence in the mammal; inserting the RNA into a vessel in the mammal, wherein the vessel consists of arteries, arterioles, capillaries, venules, sinusoids, veins, lymphatics, and bile ducts; and delivering the RNA to the cell wherein the protein production is blocked using the teachings and motivation of Kamasaka et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the antisense oligonucleotide taught by Kamasaka et al. with a RNA used for blocking protein production of Applicant's invention since the substitution of one known element for another to obtain predictable results was obvious at the time of invention. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the antisense oligonucleotide taught by Kamasaka et al. with a RNA used for blocking protein production of Applicant's invention since it is obvious to substitute one equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2114.06.

One of ordinary skill in the art would have been motivated to devise a process for delivering a RNA into a cell of a mammal to block the production of a protein comprising making the RNA consisting of a sequence that is substantially complementary to a nucleic acid sequence in the mammal; inserting the RNA into a vessel in the mammal, wherein the vessel consists of arteries, arterioles, capillaries, venules, sinusoids, veins, lymphatics, and bile ducts; and delivering the RNA to the cell wherein the protein production is blocked since Kamasaka et al. taught that such a method could be used to

inhibit and subsequently treat viral infection in a human patient. One of ordinary skill in the art would have been motivated to substitute the antisense oligonucleotide taught by Kamasaka et al. with a RNA used for blocking protein production of Applicant's invention since the substitution of one known element for another to obtain predictable results supports a rejection of obviousness under 35 U.S.C. 103.

There would be a reasonable expectation of success to devise a process for delivering a RNA into a cell of a mammal to block the production of a protein comprising making the RNA consisting of a sequence that is substantially complementary to a nucleic acid sequence in the mammal; inserting the RNA into a vessel in the mammal, wherein the vessel consists of arteries, arterioles, capillaries, venules, sinusoids, veins, lymphatics, and bile ducts; and delivering the RNA to the cell wherein the protein production is blocked since Kamasaka et al. taught the successful use and design of such a method using antisense oligonucleotides and one of ordinary skill in the art would have expected success at substituting one known element for another to obtain predictable results at the time of invention.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR

1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-

217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

tcg
June 20, 2008

/Sean R McGarry/

Primary Examiner, Art Unit 1635

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/007,448	LEWIS ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	